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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/362,598	07/28/1999	JOEL V. WEINSTOCK	3948/79934	7062

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PALMER & DODGE, LLP
KATHLEEN M. WILLIAMS
111 HUNTINGTON AVENUE
BOSTON, MA 02199

EXAMINER	
ZEMAN, ROBERT A	

ART UNIT	PAPER NUMBER
1645	24

DATE MAILED: 03/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/362,598	WEINSTOCK ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 25 February 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *see attached*.

3. ☒ Applicant's reply has overcome the following rejection(s): *none*.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: none

   Claim(s) objected to: none

   Claim(s) rejected: *24,26 and 28-32*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

ADVISORY ACTION

The amendment filed 2-25-2003 under 37 CFR 1.116 in reply to the final rejection has been considered but is not deemed to place the application in condition for allowance and will not be entered because: The proposed amendment raises new issues that would require further consideration and/or search.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 24, 26 and 28-32 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of determining the immune response the co-infection of mice with *M. avium* and *S. mansoni* (either with or without TNBS treatment) or the infection of mice with *T. muris* (with TNBS treatment) by determining the amounts of IL-4, IL-5 and IFN-γ, does not reasonably provide enablement for a method of screening an helminthic parasite preparation for one or more components that reduce excessive Th1 immune responses, wherein said preparation is prepared by fractionating and sub-fractionating the helminthic preparation is maintained for reasons of record. The specification still does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant argues:

1. Homogenization is discussed on page 18, line 25 to page 19 line 11 of the specification.

2. Fractionating is defined in the specification as "the process of dividing a helminthic homogenate or fraction of a homogenate into smaller sub-portions or fractions on the basis of some physical, chemical or biochemical property" (page 9, lines 17-19).

3. Sub-fractioning is defined in the specification as subjecting a fraction to a further step of fractioning (page 8, lines 19-23).

4. The specification states that the fractionation can be performed using one or more chromatographic techniques which are defined (at page 9, lines 20-22) as "a technique that separates components of a mixture based on size, charge, molecular weight, hydrophilic/hydrophobic interactions, solvent interactions and/or specific binding interactions" and that such techniques include column chromatography, HPLC, FPLC, matrix-affinity, chromatography, reverse-phase chromatography and electrophoretic separation.

5. Fractions and sub fractions can be obtained by any method known in the art and preferred by the one practicing the invention.

6. Predictability of the activity of embodiments that may be embraced within the claims is note a requirement of the statute.

7. The claimed methods are drawn to methods of screening the helminthic parasite preparations for the ability to reduce an excessive Th1 immune response.

8. The fractions and sub fractions can be assayed for activity (i.e. reducing an excessive Th1 immune response) utilizing assays described on page 21, line 21 to page 22, line 16 of the specification.

9. Infection of mice is illustrated in Example 1.

10. Down regulation of an ongoing Th1 response is shown in Example 2.

11. Attenuation of a Th1-type gut inflammation in mice by treatment of helminthes is shown in Example 3.

12. Down modulation of Crohn's disease in humans is shown in Example 6.

13. Down modulation of ulcerative colitis in humans is shown in Example 7.

14. Protection against multiple sclerosis in mice is shown in Example 8.

15. The specification provides ample guidance on the assays in which said fractions and sub fractions can be used.

16. Sufficient guidance is provided to enable one of ordinary skill in art to perform the "assay step" *in vivo*.

17. The specification provides sufficient guidance with regard to what parameters and markers are measured, how they are measured and how the samples are obtained.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Points 1-5, the Office agrees with Applicant's assertion that the methods of obtaining fractions and sub-fractions claimed in the instant claims constitute methods known in the art and hence would have been obvious to one of ordinary skill in the art. However, said methods are not sufficient to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

With regard to Points 6-8 , while the specification prophetically discusses the testing of sub-fractions, it does not disclose how said **sub-fractions** were used in the assay. Moreover, the specification does not provide guidance as to which biological functions (other than IL-4, IL-5 and IFN-γ production) should be tested or how the testing of said functions would result in identifying "one or more components that reduce an excessive Th1 response".

With regard to points 16 and 17, the specification is silent on how one would perform the "assay" step of the claimed methods *in vivo*. The specification provides no guidance on what parameters or markers are measured, how said parameters or markers are measured or even how samples are obtained. Given the total lack of guidance provided by the specification showing sub-fractionation of preparations and how one would perform the claimed method *in vivo*, it would require undue experimentation by one of skill in the art to make and use the invention commensurate in scope with the claimed subject matter.

With regard to Points 9-15, the working examples cited do not apply to the instant invention as they exemplify the use of intact ova not the *in vivo* screening of helminthic fractions or sub-fractions. All the disclosed assays were performed *in vitro*.

Therefore, for the reasons set forth above the specification is only enabling for an *in vitro* method of determining which helminthic fractions or sub-fractions can affect the an immune response in mice co-infected with *M. avium* and *S. mansoni* (either with or without TNBS treatment) or the infection of mice with *T. muris* (with TNBS treatment) by determining the amounts of IL-4, IL-5 and IFN-γ.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 26 and 32 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons of record.

Claim 26 is still rendered vague and indefinite by the use of the phrase "one or more further steps of fractionating and assaying. Contrary to Applicant's argument, said claim is not merely broad but is indefinite. It is unclear what steps would fall under the limitation of "a fractionating and assaying" step. It is equally how one can have **one step** that both "fractionates" and "assays". As written it is still impossible to determine the metes and bounds of the claimed invention. It should be noted that the amendment, had it been entered, would have been sufficient to overcome said rejection.

Claim 32 is still vague and indefinite since it is unclear how one would assay activity *in vivo*. Applicant argues that said claim encompasses all assays that are performed *in vivo* to detect a reduction in an excessive TH1 immune response.

Applicant argues:

1. Infection of mice is illustrated in Example 1.
2. Down regulation of an ongoing Th1 response is shown in Example 2.
3. Attenuation of a Th1-type gut inflammation in mice by treatment of helminthes is shown in Example 3.
4. Down modulation of Crohn's disease in humans is shown in Example 6.
5. Down modulation of ulcerative colitis in humans is shown in Example 7.

6. Protection against multiple sclerosis in mice is shown in Example 8.

7. The specification provides ample guidance on the assays in which said fractions and sub fractions can be used.

8. Sufficient guidance is provided to enable one of ordinary skill in art to perform the "assay step" *in vivo*.

9. The specification provides sufficient guidance with regard to what parameters and markers are measured, how they are measured and how the samples are obtained.

Applicant's arguments have been fully considered and deemed non-persuasive.

Said claim not only fails to identify what, if any, assays would be considered an "*in vivo* assay" to detect a reduction in an excessive TH1 immune response, but fails to recite the active steps required in order to fulfill the stated objective of the method claim. Moreover, the working examples cited do not apply to the instant invention as they exemplify the use of intact ova not the *in vivo* screening of helminthic fractions or sub-fractions. All the disclosed assays were performed *in vitro*.

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was

commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The instant claims are drawn to a method of screening a helminthic preparation for one or more components that reduce an excessive Th1 immune response. The method comprises preparing and fractionating the preparation and assaying the products for the ability to reduce an excessive Th1 immune response.

The rejection of claims 24, 26 and 28-32 rejected under 35 U.S.C. 103(a) as being unpatentable over Pearce et al. (Journal of Exp. Medicine, Vol.173, pages 159-166, 1991) in view of Pearce et al. (PNAS, Vol. 85, pages 5678-5682, 1988) is maintained for reasons of record.

Applicant argues:

1. Pearce et al. (1988) teaches vaccinating mice with paramyosin protein which was shown to stimulate T lymphocytes from vaccinated mice to produce lymphokines (i.e. IFNγ) and that lymphocytes from mice vaccinated with paramyosin were found to produce IFNγ in response to living schistosomula.

2. Elevated IFNγ production is an excessive Th1 immune response. Therefore Pearce et al. does not teach a method of reducing an excessive Th1 response but rather causing an excessive Th1 immune response.

3. Pearce et al. (1991), teaches vaccination of mice with attenuated larval stages of the parasite in order to reduce subsequent infection by that parasite.

4. Pearce et al. (1991) discloses that data shows enhanced IFNγ synthesis by cells from infected animals and that T cells from vaccinated mice of prepatently infected animals responded primarily with Th1 lymphokines.

5. Like Pearce et al. (1988), Pearce et al. (1991) does not teach a method of reducing excessive Th1 immune response.

6. Neither reference discloses the claimed method, nor can they be combined in such a way as to render obvious said method.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Points 2 and 5, Applicant is reminded that the instant claims are drawn to a method of screening a helminthic preparation for one or more components that reduce an excessive Th1 immune response. The method comprises preparing and fractionating the preparation and assaying the products for the ability to reduce an excessive Th1 immune response. They are not drawn to methods of reducing a Th1 immune response.

As outlined in the previous Office action, **Pearce et al. (1991)** disclose a method of identifying antigens from the helminthic parasite *Schistosoma mansoni* for the ability to reduce Th1 responses (see abstract and pages 164-165). Said method comprises preparing parasite antigens e.g. cercariae, soluble extracts of schistosomula, adult worms and eggs (see Material

and Methods section, page 160) and screening those preparation for the production of either IFNγ (Th1 response cytokine) or IL-5 (Th2 response cytokine)(see figures 1, 5 and Tables 2-3). Pearce et al. (1991), contrary to Applicant's assertion (Point 4), clearly disclose that "Th2 response in infected animals was shown to be induced by schistosome eggs and directed largely against egg antigens" (see abstract lines 10-12). Therefore, **the method disclosed by Pearce et al. (1991)** differs from the claimed invention in that they do not explicitly disclose a method of preparing an helminthic parasite antigen comprising homogenizing, separating homogenate fractions and identifying sub-fractions for biological activity. However, Pearce et al. (1988) disclose a method of preparing antigens from *Schistosoma mansoni* that comprises obtaining adult schistosomes, homogenizing in phosphate buffered saline, centrifuging and purifying by immunoaffinity chromatography (see pages 5678-5679). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare Schistosoma antigens utilizing the homogenization and immunoaffinity column chromatography disclosed by Pearce et al. (1988) and assay the resulting fractions for the ability to reduce excessive Th1 responses utilizing the assay methods disclosed by Pearce et al. (1991). It would have been expected, barring evidence to the contrary, that the purified schistoma antigens would be identified for their ability to reduce excessive Th1 responses because Pearce et al. (1991) specifically identify and compare antigens and their abilities to down regulate Th1 cytokine production. It should be noted that Applicant has maintained that the homogenization and sub fractionation of a helminthic preparation is well known in the art and hence would be obvious to one of ordinary skill in the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (703) 308-7991. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (703) 308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Robert A. Zeman
March 26, 2003